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HARVARD MEDICAL SCHOOL,
CHILDREN'S HOSPITAL, AND
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A Child with Chronic Manganese Exposure from Drinking Water

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The patient's family bought a home in a suburb, but the proximity of the house to wetlands and its distance from the town water main prohibited connecting the house to town water. The family had a well drilled and they drank the well water for 5 years, despite the fact that the water was turbid, had a metallic taste, and left an orange-brown residue on clothes, dishes, and appliances. When the water was tested after 5 years of residential use, the manganese concentration was elevated (1.21 ppm; U.S. Environmental Protection Agency reference, < 0.05 ppm). The family's 10-year-old son had elevated manganese concentrations in whole blood, urine, and hair. The blood manganese level of his brother was normal, but his hair manganese level was elevated. The patient, the 10-year-old, was in the fifth grade and had no history of learning problems; however, teachers had noticed his inattentiveness and lack of focus in the classroom. Our results of cognitive testing were normal, but tests of memory revealed a markedly below-average performance: the patient's general memory index was at the 13th percentile, his verbal memory at the 19th percentile, his visual memory at the 14th percentile, and his learning index at the 19th percentile. The patient's free recall and cued recall tests were all 0.5–1.5 standard deviations (1 SD = 16th percentile) below normal. Psychometric testing scores showed normal IQ but unexpectedly poor verbal and visual memory. These findings are consistent with the known toxic effects of manganese, although a causal relationship cannot necessarily be inferred. **Key words:** ADHD, attention deficit hyperactivity disorder, manganese, manganese exposure, water, water pollution. *Environ Health Perspect* 110:613–616 (2002). [Online 14 May 2002] <http://ehpnet1.niehs.nih.gov/docs/2002/110p613-616woolf/abstract.html>

Case Report

A 10-year-old male was referred to the pediatric environmental health center after his pediatrician discovered that he had an elevated blood manganese concentration. The child had an unremarkable past medical history; there was no history of trauma, neurologic injury, or exposure to other toxic drugs or chemicals. The family purchased their home in a Boston, Massachusetts, suburb 5 years before the clinic visit. When the house was built, its proximity to wetlands and distance from the town water main, which serviced all of the other homes in the neighborhood, prevented connecting the house to town water. Consequently, a well was drilled to supply the home with water. The family had since been drinking water from this well, despite the fact that the water was somewhat turbid and had a distinct metallic taste. Shortly after moving into the home, they noticed that clothes, dishes, and appliances, such as the dishwasher, became tinged with an orange-brown residue that

was difficult to clean. Special filters fitted to the well were expensive to install, required continuous maintenance, and did not improve the water significantly, according to parental report.

Four months before the clinic visit, the water was tested for contaminants (Table 1) (1–3), and iron and manganese concentrations were both elevated. It is uncertain how the water became contaminated, although the town is highly industrialized and toxic waste dumps near the home had been a concern in the past. The parents and their two sons (16 and 10 years old) subsequently had health assessments. Only the younger boy had abnormally high blood manganese concentrations. This 10-year-old child's serum manganese concentration was elevated at 0.90 µg/100 mL (reference normal, < 0.265 µg/100 mL), with a whole blood manganese concentration of 3.82 µg/100 mL (reference normal, < 1.4 µg/100 mL) (3). The family switched to bottled water for drinking, but they continued to use the well water for

cleaning, showering, and other household purposes.

Physical examination of the patient revealed a well-nourished, well-developed male without skin rashes, resting or intention tremors, or evidence of illness. A detailed neurologic examination was normal. He was fully alert and oriented and had a normal gait. There was no abnormally high muscle tone, cogwheeling, past-pointing, nystagmus, or fixed facies. The patient's balance with his eyes closed was good; however, his ability to coordinate rapid alternating motor movements was weak. His fine motor skills and reflexes were normal, and the sensory examination was unremarkable.

In a blood sample obtained 1 month after the original test, the patient's hemoglobin concentration was 12.1 g, his serum iron level was 61 µg/dL (reference range, 21–151), and his total iron-binding capacity was 327 µg/dL (reference range, 220–440). The patient's ferritin was 18 ng/mL (reference range, 10–300) and his transferrin concentration was 229 mg/dL (reference range, 174–348). The patient's whole blood manganese level was still elevated at 1.74 µg/100 mL. A 24-hr urine collection revealed elevated manganese

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excretion at 8.5 µg/L (reference normal, < 1.07 µg/L) (3) or 8.9 µg manganese/g creatinine (urine creatinine 713 mg/24 hr). The hair manganese level was 3,091 ppb of washed, acid-digested hair (reference normal, < 260 ppb hair) (4). A sample of hair from this child's older sibling also revealed an elevated manganese concentration, 1,988 ppb of washed, acid-digested hair. Hair and repeated blood samples from other family members were not obtained.

Magnetic resonance imaging (MRI) of the patient's brain revealed no attenuation in the putamen or caudate nucleus and no enhancement in the region of the globus pallidus or basal ganglia, mid-brain, or pons.

Results of a battery of neuropsychologic tests are shown in Table 2. The major findings were intact global cognitive skills but striking difficulties in both visual and verbal memory, consistent with a deficit in free retrieval skills. The patient was in the fifth grade at a local elementary school and had no history of learning problems. The mother completed the Child Behavior Checklist (CBC-Parent) and the Behavior Assessment System for Children (BASC) questionnaires, and the child's teacher filled out the Child Behavior Checklist (CBC-Teacher) and BASC Teacher Report Form. According to both parent and teacher reports, the patient's grades and behavior were excellent, although his mother acknowledged that for the past several years teachers had consistently noted a difficulty with listening skills and following directions.

The family was advised to discontinue all residential use of the water from the well. Clinic physicians interceded with town officials on the behalf of the family, so that within 3 months of the initial clinic visit, a standpipe was dropped from the water main to the family home so that the family could be serviced with town water. Eighteen months later, the patient's mother reported that he was still in an age-appropriate grade. However, his teachers continued to remark on his difficulty in remaining on task and his inattentiveness in class.

Manganese Analysis

Hair samples. About 2–3 g of hair was collected from the back of the head close to the scalp and washed. All glassware and plasticware used in the analysis were acid washed (soaked in 10% nitric acid for 24 hr and rinsed several times with deionized water). All hair samples were handled in a clean hood. Hair samples (0.14 g/sample) were sonicated for 15 min in 10 mL 1% Triton X-100 solution in a precleaned 15-mL plastic tube. After sonication, samples were rinsed several times with distilled deionized water and dried in a drying oven at 70°C for 24 hr.

Blood and hair samples were weighed and digested in 1 mL concentrated nitric acid for 24 hr; after the addition of 0.5 mL 30% hydrogen peroxide, the samples were diluted to 10 mL with deionized water. We used a dynamic reaction cell-inductively coupled plasma mass spectrometer (Elan 6100; Perkin-Elmer, Shelton, CT) (5–7) to analyze the samples. Quality control measures in our laboratory included analysis of initial calibration verification standard [standard reference material 1643d trace elements (National Institute of Standards and Technology, Gaithersburg, MD) in water], continuous calibration standards, procedural blanks, duplicate samples, spiked samples, quality control standard, and certified reference material for human hair (GBW 09101; Shanghai Institute of Nuclear Research, Shanghai, China). Results are the average of five replicate measurements. The limit of detection for this procedure is 0.2 ng/g for the analytical solution. Recovery of the analysis of quality control standard and spiked sample by this procedure is 90%, –110%, and < 5% precision.

Blood and urine samples. Blood and 24-hr urine samples were collected into acid-washed containers and analyzed by ARUP Laboratories (Salt Lake City, UT). Briefly, 0.5 mL urine was mixed with 0.5 mL 15% nitric acid; 100 ppb yttrium was added as an internal standard. This mixture was diluted to 5 mL total with deionized water. Blood was prepared in a similar manner, except that the blood/acid mixture was subjected to a heat block for 15 min at 75°C before dilution.

We used four-point calibration with appropriate controls for both urine and blood analysis. Calibration methods used were similar to those described for hair. All samples were assayed using inductively coupled plasma mass spectrometry (Elan 6100drc; Perkin-Elmer).

Discussion

Manganese is an essential cofactor in humans for antioxidant enzymes such as superoxide dismutase, but it is also toxic when ingested or inhaled in large amounts over time. Manganese is a well-known occupational toxicant, causing a depletion of brain dopamine and a syndrome of motor dysfunction and memory loss resembling Parkinson disease (8). Manganese can adopt different valences and is a powerful oxidant as the trivalent species (9). Together with dopamine, manganese can accelerate oxidation–reduction reactions, producing reactive oxidative molecules such as hydrogen peroxide and superoxide free radicals; this potentially explains the dopaminergic neurotoxicity seen in chronic manganese poisoning and the relief of symptoms by the administration of L-dopa in

some patients (10–14). With relevance to the current case, derangements in dopamine metabolism have also been invoked as a mechanism underlying the syndrome of attention deficit hyperactivity disorder in some children (15,16).

Manganese can also produce free radicals independent of dopamine (17). Excess manganese concentrates in mitochondria, where DNA is susceptible to manganese-induced oxidative injury and produces oxidant damage in selected brain regions such as the basal ganglia. In *in vitro* studies, manganese has also been found to inhibit mitochondrial aconitase enzyme activity in a dose-dependent fashion (18). Such inhibition was reversed by adding iron to the reaction mixture. Similarly, manganese selectively inhibited aconitase activity in rats in specific areas of the brain: the frontal cortex, striatum, substantia nigra, and hippocampus (18). The disruption of energy and iron metabolism in brain mitochondria may be related to the neurotoxicity observed in manganese poisoning.

Manganese and iron are thought to share many absorptive and metabolic pathways. In a study of 26 women given controlled amounts of manganese in their diets, Finley (19) confirmed a low absorption rate and low bioavailability of manganese, with an inverse correlation with body iron stores as represented by serum ferritin values. Other animal and human studies have confirmed that manganese absorption is inversely associated with hemoglobin and ferritin levels (20,21). The patient described in this paper had no evidence of iron deficiency anemia, which might have led to a more avid uptake of manganese from water.

Finley's study (19), showing poor bioavailability of dietary manganese in young women, may have limited relevance to manganese loading found in the present case. Finley's study (19) was carried out over only 60 days, with a manganese intake (in the high dietary group) of 9.5 mg/day. In the case of the child reported here, only one sample of the well water was analyzed for manganese, so that duration of its contamination is uncertain.

Table 1. Analyses of well water.

Assay	Concentration	MCL
Manganese (ppm)	1.21	0.05
Iron (ppm)	15.7	0.3
Copper (mg/L)	0.08	1.3
Lead	ND	0.015
Calcium (ppm)	37.98	NA
Magnesium (ppm)	15.9	NA

Abbreviations: MCL, maximum contaminant level; NA, not applicable; ND, not determined. All assays were performed using measurement specifications under U.S. Environmental Protection Agency (EPA) Guideline 200.7 (7). Data for the MCL for manganese from the Code of Federal Regulations (2) and reported by the Agency for Toxic Substances and Disease Registry (3).

Thus, Finley's findings (19) are probably not comparable to the situation of our patient who received up to 5 years of manganese loading from ingested water. In at least one study of infants, significant increases in hair manganese levels were found among young infants fed infant formulas containing relatively high amounts of manganese compared to hair manganese levels in infants fed breast milk, which contains relatively little manganese (22). Thus, bioavailability of ingested manganese in infants and children may be quite different from that in adults.

Subtle neurologic toxicity has been reported in epidemiologic studies of adults exposed to manganese-contaminated water. In one study of older adults living in three different locations in Greece with low (0.004–0.015 mg/L), intermediate (0.08–0.25 mg/L), and high (1.80–2.30 mg/L) levels

of manganese in drinking water, abnormal neurologic scores were associated with higher hair and water manganese concentrations (23). Although it has been speculated that chronic low-level exposure to excess manganese may be detrimental to children, whose neurologic plasticity may increase susceptibility to manganese, documentation of such toxicity is sparse. The severity of functional disturbances would likely be related both to cumulative manganese dose and the duration of exposure, as well as to individual variations in susceptibility, although detailed psychometric testing of environmentally exposed children has not been previously performed. In one study of 92 pairs of Chinese children 11–13 years of age, one-half of whom had been exposed to elevated manganese concentrations in drinking water (0.241–0.346 mg/L), exposed children had

lower scores on tests of short-term memory, manual dexterity, and visuo-perceptual speed than did unexposed children (24).

Previous research has suggested that in manganese poisoning blood or urine manganese concentrations may be transiently elevated, but these elevated concentrations often do not correlate well with evidence for toxic body burdens or adverse clinical effects. Thus, their utility in the clinical assessment of manganese-exposed patients has been questioned. Such considerations might explain why this child's blood levels were high, whereas those of other family members who drank the same water were not. However, hair manganese concentrations may more accurately reflect chronic exposures and may correlate more closely with toxic effects on learning ability. For example, in one study, Pihl and Parkes (25) found elevated hair manganese concentrations among 31 learning disabled children compared to 22 controls matched for age, sex, socioeconomic status, and ethnic origin. In a second case-control study, Collipp et al. (22) found higher hair manganese levels (mean, 0.434 µg/g) in 16 children 7–10 years of age who had been defined by the school as hyperactive and learning disabled, and lower hair manganese levels (mean, 0.268 µg/g) in 44 age- and sex-matched controls from the same school. A more recent pilot study also found evidence that subjects with attention deficit hyperactivity disorder have significantly higher levels of manganese in head hair than age and demographically matched controls (26). In the case reported in this paper, both the patient and an older sibling had elevated hair manganese concentrations, which is consistent with a chronic poisoning involving the entire family, despite the normal blood levels seen in other family members. Alternatively, the habits of family members who drank bottled water compared to others, including the index case, who often drank tap water may explain such apparent differences in exposure.

In the current case, we found a marked discrepancy between intact global cognitive skills and specific deficits in visual and verbal memory. These deficits, although substantial in magnitude, did not appear to be seriously affecting this child's classroom performance at present, although for the past several years his teachers have consistently noted a difficulty with the patient's listening skills and his ability to follow instructions. Whether the cognitive impairments discovered in this child are attributable specifically to manganese toxicity cannot be proven with assurance, although no other toxic exposures, past medical history, or alternative explanations for this child's impairments were forthcoming.

Table 2. Results of psychometric testing.

Scale	Standard score	Percentile	90% CI
Wechsler Intelligence Scale for Children			
Full-scale IQ	106	66	101–110
Verbal	110	75	104–115
Performance	102	55	95–109
Verbal comprehension	110	75	104–115
Wide Range Assessment of Visual-motor Abilities			
Drawing	103	58	93–113
Matching	101	53	89–113
Pegboard	114	83	100–128
Visual-motor composite	108	70	87–119
Wisconsin Card Sorting Test			
Total errors	118	88	
Perseveration responses	119	90	
Perseveration errors	119	90	
Nonperseveration errors	112	79	
Percent conceptual level	121	92	
Wide Range Assessment of Memory and Learning			
General memory index	83	13	77–89
Verbal memory index	87	19	79–95
Visual memory index	84	14	74–94
Learning Index	87	19	78–96
California Verbal Learning Test—Children's Version ^a			
Level of Recall			
List A trial 1 free recall	–1.0		
List A trial 5 free recall	–1.5		
List B free recall	–1.0		
List A short-delay free recall	–0.5		
Short delay free recall vs. List A trial 5	1.0		
List A short-delay cued recall	–0.5		
List A long-delay free recall	–1.5		
List A long-delay cued recall	–1.0		
Learning Characteristics			
Semantic cluster ratio	0.5		
Percent total recall from primacy region	2.0		
Percent total recall from middle region	–3.0		
Percent total recall from recency region	1.5		
Recall Errors			
Perseverations (free and cued recall)	–1.0		
Intrusions (free and cued recall)	–1.0		
Free-recall intrusions	–0.5		
Cued-recall intrusions	–1.0		
Recognition Measures			
Discriminability	0.5		
Recognition discrimination vs. long-delay free-recall	2.0		

CI, confidence interval.

^aStandard scores expressed as standard deviation units; for example, 0.0 is the expected score, and –1.0 is a score 1 SD below expected (i.e., < 16th percentile for age).

Although clinicians have attempted to chelate adults suffering from chronic occupational manganese poisoning, evidence for the effectiveness of chelation therapy in either reducing total body burdens of manganese or reversing symptoms of neurologic toxicity is lacking (27). Because chelation may theoretically mobilize stores of manganese and exacerbate its toxicity by increasing its transport across cell membranes, such therapy poses risks and should not be undertaken lightly. We chose not to use such medications in the management of this child in the absence of clinical studies of their effectiveness and in light of our concerns that such therapy engendered an unacceptable risk of toxicity.

The recent introduction of a new gasoline additive, methylcyclopentadienyl manganese tricarbonyl (MMT), into the marketplace raises the possibility of increased releases of manganese into the environment, with the likelihood of greater exposures of children to this metal by chronic inhalation (28). The implications of this new environmental contaminant for the health of children must be carefully weighed. This case should prompt further investigation of the relationship between chronic manganese dosing of children and deleterious effects on neurodevelopmental and neurobehavioral outcomes. We conclude that psychometric studies of children inadvertently exposed to manganese are warranted and that further study is needed to determine doses at which low-level environmental exposures to manganese may be harmful to children.

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